

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

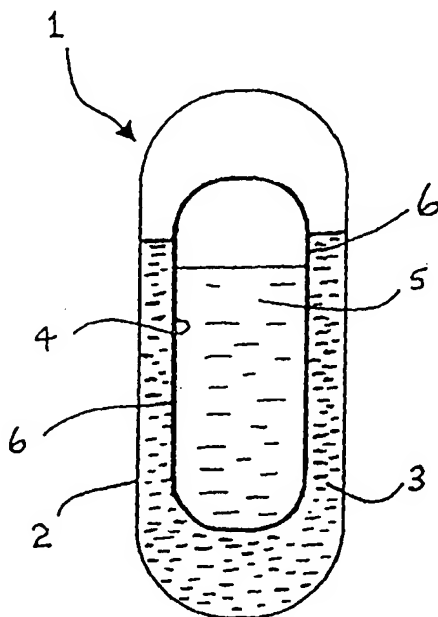
(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
31 January 2002 (31.01.2002)

PCT

(10) International Publication Number
WO 02/07710 A2

- (51) International Patent Classification⁷: **A61K 9/48** (74) Agent: **BRITTER, Keith, Palmer**; Britter and Co., Enterprise House, 14b Whitehorse Street, Baldock, Hertfordshire SG7 5QN (GB).
- (21) International Application Number: **PCT/GB01/03247**
- (22) International Filing Date: **19 July 2001 (19.07.2001)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:
0017673.5 20 July 2000 (20.07.2000) GB
0028335.8 21 November 2000 (21.11.2000) GB
- (71) Applicant (for all designated States except US): **MW EN-CAP LIMITED** [GB/GB]; 4 Dunlop Square, Livingston, West Lothian EH54 8SB (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **BAKHSHAEI, Massoud** [IR/GB]; 1102 Pollockshaws Road, Glasgow G41 3XA (GB). **BOWTLE, William, John** [GB/GB]; 2 Netherwood Park, Livingston, West Lothian EH54 8RN (GB). **MCNAUGHTON, Alyn, Brandon** [GB/GB]; 40 Fiddich Drive, Livingston, West Lothian EH54 9HG (GB).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DELIVERY DEVICE



(57) Abstract: An active principle delivery device (1) comprising an inner capsule (4) within an outer capsule (2), the inner and outer capsules (4, 2) containing the same active principle (5, 3), with at least the outer capsule (2) being a hard capsule and the active principle (3, 5) in at least one of the capsules (2, 4), comprising a fluid. Also provided is a method of fabricating such a delivery device (1), as well as a method of controlling the pharmacokinetic profile of an active principle.

WO 02/07710 A2

WO 02/07710

PCT/GB01/03247

-1-

DELIVERY DEVICEDESCRIPTION

5 This invention relates to a delivery device and
a method of delivering a substance to at least one
location, more particularly the invention relates to
a delivery device comprising one or more capsules
within an outer capsule, with at least two of said
10 capsules containing the same active principle and a
method of delivering that active principle.

Capsule technology has been developing for over
one hundred years and is now at the stage where many
15 medicaments are formulated so as to be encapsulated
within a gelatin capsule. The benefits of such
formulations reside in the fact that the capsules
are often easy for a patient or other consumer to
swallow or use and the capsule can contain a large
20 amount of the particular medicament for delivery to
the individual, the actual capsule dissolving in the
stomach or other part of the intestinal tract.

Indeed, to ensure that a particular medicament
25 is delivered to the desired site, a large amount of
research has been carried out in coating techniques.
Such techniques are used to control or at least vary
the time or location of dissolution of the capsule
and, consequently, the time or location of release
30 of the medicament.

WO 02/07710

PCT/GB01/03247

- 2 -

Several known techniques have been developed for the administration of more than one active principle at a time or at short intervals whilst the active principle is in tablet form. In those cases, 5 coatings are also used to vary or control the release time or location of that active principle.

US 1815902 (Ellzey) discloses a double capsule, with one capsule within the other, for administering 10 medicaments in which an inner hard gel capsule contains medicament, whilst an outer hard gel capsule contains an innocuous alkaline material.

FR 1454013 (Pluripharma) relates to another type 15 of double capsule with different medicaments, in solid form, in the inner and outer capsules which are made of hard gel, whilst DE 2729068 (Liedtke) is directed to a double capsule in which the same or different active principles in solid form are 20 provided in inner and outer hard gel capsules, with any liquids being provided solely in inner and outer soft gel capsules.

In FR 2524311 (Azalbert), there is described 25 another double capsule for the ingestion of medicinal agents which are different and incompatible with one another. The inner and outer capsules are of hard gel, with the medicinal agents possibly being in liquid form.

30

EP 0116311 (Morishita Jintan Co et al) teaches a double soft gel capsule with the inner and outer

WO 02/07710

PCT/GB01/03247

- 3 -

capsules containing different medicines, whilst EP 0130163 (Pharmacia) discloses a double capsule with the inner capsule containing an allergen and the outer capsule containing an antiallergie substance.

5

US 5310555 (Zimmer) is directed to a method of delivering incompatible and different compounds in vivo, with live intestinal or rumen microorganisms in an inner capsule and a nutritional supplement in an outer shell in which the inner capsule is contained.

EP 0624365 (ASTA Medica) describes a form of double capsule arrangement in which an outer sheath has bioadhesive properties and contains a capsule containing at least one hygroscopic substance and non-liquid active agent tablets.

WO 95/10262 (RP Scherer Corporation) relates to a controlled release device for delivering a liquid substance to a patient, wherein different materials are contained in a double capsule. The liquid substance is contained in an inner soft or hard gel capsule and an inert solid excipient is contained in an outer hard gel capsule, with a water-swella-
ble material in the outer capsule for causing disengagement of the capsules upon exposure to an aqueous medium.

WO 99/30693, AXCAN PHARMA shows that it is possible to provide a double capsule for the administration of active medicaments in multiple

WO 02/07710

PCT/GB01/03247

- 4 -

therapies. This disclosure considers the possibility of treating a microorganism, such as *Helicobacter pylori*, with known solid medicaments in a double capsule.

5

The multiple capsule delivery devices discussed above show that is known to provide double, triple and, sometimes, quadruple therapies for the treatment of many conditions, wherein the inner and
10 outer capsules can be provided in certain, but not all, combinations of solid and soft get capsules containing the same or different active principles in solid or liquid form.

15 However, none of the prior art delivery devices discussed above ever discloses, whether directly or by implication, the use of the same active principle as a fluid, such as liquid or semi-solid, in a particular multiple capsule format for the treatment
20 of a plurality of conditions.

Also, these known multiple capsule delivery devices provide treatment regimes which are limited, as it has been found to be difficult to control and
25 vary the posologies, particularly when solid active principles are employed. Indeed, it is known also that certain active principles are not amenable to patients in solid form and it is well established that the most effective dose of most medicaments
30 occurs when the active principles are in liquid form, for example, as an aqueous solution, suspension, micelle or emulsion.

WO 02/07710

PCT/GB01/03247

- 5 -

Accordingly, it is an object of the invention to provide a delivery device which overcomes the problems associated with the known devices of the prior art discussed above. It is also an object to
5 provide a delivery device which can be used in the treatment of a plurality of conditions, where at least one desired form of active principle is fluid and where it is desired to control both the release rate and site of release of the active principle.

10

Thus, a first aspect of the invention provides an active principle delivery device comprising an inner capsule within an outer capsule, wherein:

15 the inner and outer capsules contain the same active principle;

at least the outer capsule is a hard capsule;
and

20

the active principle in at least one of the capsules comprises a fluid (as hereinafter defined)

A second aspect of the invention resides in a
25 method of fabricating an active principle delivery device, comprising:

providing a first capsule and a second capsule of which at least the first capsule is a hard
30 capsule;

WO 02/07710

PCT/GB01/03247

-6-

placing the same active principle in each of the first and second capsules, with the active principle in at least one of the capsules comprising a fluid (as hereinafter defined); and

5

placing the second, active principle-containing, capsule within the first, active principle-containing, hard capsule.

10 In a third aspect of the invention, there is provided a method of controlling the pharmacokinetic profile of an active principle comprising:

determining the most efficacious site of active
15 principle release;

placing an active principle in a first hard capsule;

20 placing the same active principle in a second capsule within the active principle-containing, first hard capsule, with the active principle in at least one of the first and second capsules comprising a fluid (as hereinafter defined), to
25 provide a delivery device;

delivering the delivery device to the predetermined active principle release site; and

30 controlling the release of the active principle at the site.

WO 02/07710

PCT/GB01/03247

- 7 -

In preferred embodiment to be described hereinbelow, the active principle is medicinal and/or nutritional.

5 Throughout this specification, the term "fluid" or derivatives thereof is used to describe a material which is a liquid or a semi-solid but not a gas, a liquid being defined as a material which flows under ambient conditions without external
10 influences, whilst a semi-solid is defined as a material or mixture of material which has a consistency that varies according to its conditions within an ambient range and which may have characteristics of both a liquid and a solid.
15 Examples of semi-solids include creams, pastes, ointments, suspensions, emulsions, thixotrope and waxes. Changes in ambient conditions, such as a temperature change, could alter a semi-solid to a more liquid state, whilst agitation, such as
20 shaking, could change a thixotrope from a more solid state to a more liquid state.

At least a portion of the active principle may be a fluid either at or immediately prior to its
25 time of use or during its manufacture

Although the first, outer capsule is a hard capsule, the second, inner capsule may be a hard or soft capsule and each may be constructed from, for
30 example, gelatin, plasticised gelatin, hydroxy propyl methyl cellulose (HPMC), starch or agar. Each of the inner and outer capsules may be coated or

WO 02/07710

PCT/GB01/03247

- 8 -

uncoated. In a preferred embodiment, the second inner capsule is a hard capsule and the active principle in both the inner and outer capsules comprises a fluid.

5

Preferably, the fluid is a liquid which may be a solution or suspension and may comprise suspended solids which may be a powder, pellet, or granules and which may be coated or uncoated. The liquid may also be thermosoftening. At least one of the capsules may contain the same active principle in more than one phase, for example, liquid, semi-solid and/or solid phases.

15 The delivery device may comprise more than one second, inner capsule within the first, outer capsule, the second, inner capsules being arranged in parallel and/or in series.

20 In a preferred embodiment, the delivery device provides a pharmaceutical dosage form for the administration of the same active principle in single therapies.

25 Also, the device may comprise an activator or co-reactant for the active principle.

The various aspects of the invention will now be described by way of example only, and with reference to the accompanying drawings in which:

30

WO 02/07710

PCT/GB01/03247

- 9 -

Figure 1 is a section through a first embodiment of delivery device;

Figure 2 is a section through a second
5 embodiment of delivery device;

Figure 3 is a section through a third embodiment of delivery device; and

10 Figures 4A to 4D are example representations of pharmaco-kinetic profiles.

Referring firstly to Figure 1, a double capsule delivery device, indicated generally at 1, comprises
15 a first, outer hard capsule 2 containing a liquid active principle 3 and a second, inner hard capsule 4 which also contains the same liquid active principle 5 as that contained in the outer hard capsule 2 and may be coated, as shown at 6.

20

Similarly, Figure 2 illustrates a triple capsule delivery device, indicated generally at 11, which comprises a first, outer hard capsule 12 containing a liquid active principle 13 and a
25 second, inner hard capsule 14 which also contains the same liquid active principle 15 as that contained in the outer hard capsule 12 and may be coated, as shown at 18. The second, inner hard capsule 14 also contains a third, inner hard capsule
30 16 which, in turn, contains the same active principle as that contained in the first and second, outer and inner hard capsule 12 and 14 but in solid

WO 02/07710

PCT/GB01/03247

- 10 -

particulate form. That second, inner hard capsule 14 may also be coated, as shown at 19. The capsules 12, 14 and 16 are in series with each other.

5 Referring now to Figure 3, a multiple capsule delivery device, indicated generally at 21, comprises a first, outer hard capsule 22 containing a liquid active principle 23 and four inner hard capsules 24 containing an active principle 25 which
10 is the same as that contained in the first, outer capsule 22 but in semi-solid form. The four inner capsules 24 are in parallel with each other but in series with the outer capsule 22.

15 Each capsule 2, 4; 12, 14, 16; 22, 24 may be filled using standard capsule-filling technology, such as intermittent or continuous motion capsule filling machines equipped with dosators, to place the same active principle therein. Similar
20 technology may be used to place the inner capsules 4; 14, 16; 24 within the respective outer capsules 2, 12, 22.

Although the first outer capsule 2, 12, 22 is a
25 hard capsule, as are the inner capsules 4; 14, 16; 24 in the three embodiments described above, the inner capsules 4; 14, 16; 24 may be soft capsules. However, any combination of hard and soft inner capsules may be employed. Also, although the first,
30 outer hard capsule 2, 12, 22 of those three embodiments contains the active principle as a liquid, it need not necessarily, as long as at least

WO 02/07710

PCT/GB01/03247

- 11 -

one of the outer capsules 2, 12, 22 and the inner capsules 4; 14, 16; 24 contains the active principle as a liquid.

5 The outer hard capsule 2, 12, 22 may be made from any suitable material which will depend upon application requirements. Such materials may include hard gelatin, hydroxy propyl methyl cellulose (HPMC) and starch, whilst any inner
10 capsule 4; 14, 16; 24 which is hard may be made from such a material. Alternatively, and if any inner capsule is a soft capsule, then such may be made from soft gelatin or agar.

15 It is well established in the medical treatment of ailments, in particular, human ailments, that there are two important thresholds for drugs. The first threshold is the therapeutic threshold, which may be defined as the concentration of active
20 principle at which the principle shows a therapeutic effect on the particular ailment. The second such threshold is the toxic threshold, which occurs when the amount of drug reaches a concentration at which the person who has ingested the drug is, or at least
25 starts to become, poisoned thereby. This effective concentration range between the therapeutic and toxic thresholds may be defined as the activity window.

30 Active principles, once released, are normally absorbed by the body where they are either metabolised or excreted. Obviously, the balance

WO 02/07710

PCT/GB01/03247

- 12 -

between release/absorbance rate and removal rate (for example, the sum of the rates of excretion and metabolism) provides the so-called pharmacokinetic profile of a particular active principle.

5 The pharmacokinetic profile for a particular active principle may be non-ideal. For example, the concentration of active principle at the desired site may rapidly fall below its therapeutic threshold once released. Alternatively, and as is
10 more usual, the concentration of the drug may slowly reduce to below the therapeutic threshold before sufficient time has elapsed for the active principle to yield the desired result.

15 A solution to this low active principle concentration problem is simply to administer more of the active principle. However, whilst this may increase the concentration of the active principle and concomitantly the time that the patient's blood
20 contains above the therapeutic threshold, it may also increase the concentration above the toxic threshold, consequently poisoning the person to whom the drug was administered. Indeed, some active principles have very small activity windows and
25 therefore administering large doses of the active principle is undesirable. In such cases, it is usual to prescribe complicated administration regimes wherein a patient is forced to take a large number of relatively small dose drugs frequently. Such
30 regimes are costly and difficult to administer, act to limit or control the patient's freedoms and,

WO 02/07710

PCT/GB01/03247

- 13 -

moreover, may be difficult to ensure patient's compliance therewith.

With regard now to Figure 4A, there is shown a
5 pharmaco-kinetic profile W of active principle concentration against time for a particular active principle. The curve W is found after administration of an active principle, in a single therapy, in the form of the delivery device 1, shown in Figure 1.

10

The delivery device 1 comprises the outer hard capsule 2 which contains the liquid active principle 3 and which is uncoated and the inner capsule 4 which also contains the same liquid active principle
15 5 and which is provided with an enteric or erodible coating 6. Once ingested, represented by R_1 , the outer capsule 2 is quickly broken down and the contents 3 made available, showing an increase in the concentration of the active principle. The
20 coating 6 on the inner capsule 4 prevents immediate release of the contents 5 thereof. However, over time the coating breaks down and, at R_2 , the contents 5 are released and therefore made available to the body. The effect, as shown in Figure 4A, is a
25 superposition of two active principle concentration curves to provide the composite pharmaco-kinetic profile W shown.

In Figure 4A, the active principle 3, 5 has a
30 relatively long absorption half-life, which is to say that it is slowly absorbed by the body. In contrast, Figure 4B shows a situation wherein the

WO 02/07710

PCT/GB01/03247

-14-

active principle 3, 5 has a short absorption half-life and is rapidly absorbed (and eliminated) by the body. A delivery device 1, such as that shown in Figure 1, may be used and again, the inner capsule 4
5 is coated at 6 to prevent early release of the active principle 5 contained therein. As can be seen in Figure 4B, the superposition of the two active principle concentration curves provides a composite pharmaco-kinetic profile X showing the pulsed
10 release of the principle 3, 5. The activity window AW of the same principle 3, 5 is also indicated (AW = toxic threshold (To) - therapeutic threshold (Th)). Such a formulation, as is contained within the delivery device 1, allows for continual
15 administration of an efficacious dose whilst the patient only has to take a single capsule.

Obviously, a delivery device 11 such as that shown in Figure 2 could also be configured to
20 provide pulsed release of a principle. In such a device 11 the intermediate capsule 14 may be coated at 18 to prevent immediate release, as may the inner capsule 16 at 19, the effect being a "three-pulse" system in which the active principle 13, 15, 17 is
25 delivered, or at least made available, in a controlled fashion. Moreover, with a surreptitious choice of coatings 18, 19, a so-called "parallel" device 21 as shown in Figure 3 could also be used.

30 Figure 4C shows a composite pharmaco-kinetic profile Y in which sustained release of the active principle is described. The delivery devices 11, 21

WO 02/07710

PCT/GB01/03247

- 15 -

may be arranged to provide such a profile Y. In some cases, a large dose of a principle is required although the body may not respond positively to a large immediate dose. Thus the active principle concentration is "ramped-up" slowly by sequential release of active principle from sequential breakdown of the capsules. In Figure 4C, three releases R_{21} , R_{22} , R_{23} are indicated. With certain medicaments, the toxicity threshold T_o may increase once the body has adjusted to the initial dose. In such circumstances, it is beneficial to provide sequential release of the active principle, taking advantage of the patient's increased tolerance thereof.

15

Figure 4D shows a representation of a further composite pharmaco-kinetic profile Z in which two releases R_{31} , R_{32} are indicated. The first release R_{31} shows a rapid rise in active principle concentration which equally rapidly dies away, the second release R_{32} providing a sustained release of active principle. This matched acute and chronic release profile provides a composite pharmaco-kinetic profile Z in which the patient is exposed to a large initial concentration of active principle followed by a sustained increase in active principle concentration. Such a profile Z may be desirable in circumstance where the initial dose primes the patient for a more sustained dose. Both serial and parallel devices 1, 11, 21 may be utilised to provide such a profile, with careful consideration being given to the choice of coatings 6; 18, 19

30

WO 02/07710

PCT/GB01/03247

-16-

which could be applied to any or all of the capsules
2, 4; 12, 14, 16; 22, 24.

The Figures 4A to 4D show particular pharmaco-
5 kinetic profiles W, X, Y and Z. It will be
understood by the skilled addressee that many
desired profiles are achievable. For example, it is
a simple matter to provide, or at least closely
approximate, a steady-state active principle
10 concentration, which is to say an invariant
pharmaco-kinetic profile over time, the rate of
removal being equal to the rate of
release/absorption of active principle. In such a
fashion, the gastrointestinal (GI) tract, or at
15 least a portion thereof, may be subjected to an at
least approximately constant concentration of active
principle as a delivery, device 1, 11, 21 travels
therealong, releasing its active principle.
Alternatively, a certain portion of the GI tract may
20 be subjected to a steady-state concentration whilst
another portion is subjected to a pulse of active
principle, for example.

The above discussion has been silent as to the
25 most efficacious site of principle delivery. The
delivery devices 1, 11, 21 can be used to deliver
their contents to the most efficacious site in the
gastrointestinal (GI) tract. For example, certain
active principles may not be best suited for uptake
30 from the acidic conditions prevalent in the stomach
and may be best suited for up-take in the colon. In
such circumstance the capsules can be coated such

WO 02/07710

PCT/GB01/03247

- 17 -

that they are only slowly dissolved under strongly acidic conditions, thereby bypassing the stomach.

Moreover, it may be desirable to deliver an
5 active principle to more than one site in the GI tract, for example the stomach and the colon. For such a delivery regime, the inner capsule 4 may be provided with a coating which slowly dissolves once exposed to the conditions of the stomach, the outer
10 capsule 2 having been dissolved soon after ingestion. In this case, the coating is arranged to dissolve, under the prevailing conditions, in the time taken for the device 1 to travel from the stomach to the desired delivery site. A typical
15 release profile may be shown by the pharmaco-kinetic profile Z of Figure 4D in which the first release R_{31} occurs in the stomach and the second release R_{32} occurs further down the GI tract, for example in the colon. As is shown, the active principle
20 concentration in the stomach and colon of the active principle are distinct due to the differing environmental conditions, the desired treatment regime and the efficacy of the active principle in each location.

25

An example of the potential uses of such a regime is in the treatment of excess dissolved intestinal gases. Intestinal wind is, in the main, caused by the swallowing of air whilst eating and
30 drinking together with the small amount which is formed through the bi-products of bacterial digestion within the stomach and GI tract. These

WO 02/07710

PCT/GB01/03247

- 18 -

gases become dissolved in the stomach contents and can cause discomfort, in some cases pain, and embarrassment. The usual way to treat such an ailment is to provide medicaments such as
5 simethicone or dimethicone which reduce the surface tension of the stomach GI tract contents, allowing the dissolved gases to come out of solution and be released from the body. Whilst the problem of dissolved gases can be addressed in the stomach it
10 is conventionally relatively difficult to treat the problem lower in the GI tract without using high doses. The delivery device 1 may be used to do so, in the manner discussed above with a lower dose of the active principle.

15

A further method of altering the release rate, and thus the absorbance profile, of an active principle, is to provide the same active principle in a two or more different and distinct phases, for
20 example solid and liquid within a single capsule. For example, the delivery device 1 of Figure 1 may comprise an uncoated outer capsule 2 in which is situated a liquid active principle 3 and a coated inner capsule 4. The inner capsule 4 may contain the
25 same active principle 5 in, for example, an aqueous liquid formulation and a coated solid, such as pellet, formulation. The encapsulated active principle could also be thermosoftening, which is to say that as the temperature increases the viscosity
30 of the active principle decreases.

WO 02/07710

PCT/GB01/03247

- 19 -

Once the outer capsule 2 has dissolved and the contents 3 thereof have been absorbed, the inner capsule 4 starts to dissolve. Once this has occurred the aqueous liquid formulation of the active principle 5 is rapidly absorbed whilst the coating on the pellets is dissolving. As that coating dissolves, the solid formulation of the active principle is absorbed by the patient providing a double pulse and sustained release composite pharmacokinetic profile.

Such delivery devices 1; 11; 21 may also be used to separate immiscible components. For example, in certain therapies it is beneficial to deliver the same active principle in a variety of solvents. Such solvents may be water and lipids or fats, the inner capsule 4 containing, for example, an aqueous liquid formulation of the active principle 5 and the outer capsule 2 containing a lipidic formulation of the same active principle 3. These same principles 3, 5 may be delivered to the same or different sites within the body as the treatment necessitates and which delivery sites may be controlled by a coating on the capsules 2, 4.

25

Thus, it can be seen that with an adroit choice of coating and/or by consideration of the capsules dissolution profile, which is to say the rate at which the capsule dissolves, the delivery device 1; 11; 21 can be arranged to provide the desired pharmacokinetic profile for treatment of a particular ailment. This can also be augmented by

30

WO 02/07710

PCT/GB01/03247

- 20 -

the provision of the same active principle in a particular phase or in particular phases within each capsule. The provision of serial and parallel arrangements of capsules within a delivery device
5 may also be utilised to control or vary the release of active principle.

In further embodiments, the delivery device, for example 1, may comprise further active
10 principles together with the same primary principle. For example, the outer capsule 2 may contain a main active principle 3 together with another, second active principle, whereas inner capsule 4 may contain the same main active principle 5 and a
15 further, third active principle, main principles 3 and 5 being the same in the same or different phases. The above-identified second and third active principles may inhibit each others activity or it may be desirable to treat a different site within
20 the GI tract with each or they may act synergistically in an undesired fashion. The delivery device 1 affords a clinician the ability to provide all three principles in one delivery device, whilst pre-determining the active principle release
25 profiles and the site of release. This leads to directed treatment of one or more specific ailments, allowing medical staff to accurately target delivery sites and ensure that the active principle concentration is optimum.

30

It is known that different shell materials exhibit a wide-range of properties. For example,

WO 02/07710

PCT/GB01/03247

-21-

gelatin capsules show an excellent resistance to oxygen penetration but are readily embrittled by the loss of moisture therefrom. However, HPMC capsules are readily penetrated by oxygen whilst being very resistant to moisture embrittlement. Therefore, an oxygen sensitive active principle could be encapsulated within an inner gelatin capsule 4 which is in turn encapsulated within an outer HPMC capsule 2 containing, for example, a non oxygen sensitive formulation. The HPMC outer capsule 2 provides a flexible tough outer shell whilst the brittle inner gelatin capsule 4, which is protected by support from the surrounding active principle, provides protection against oxidation of its contents.

15

It has been demonstrated that the delivery devices 1; 11; 21 allow for a flexibility of delivery of an active principle. By a simple choice of capsule materials, together with manipulation of capsule coating and or formulation of the active principle it is possible to accurately and precisely target active principle delivery site and concentration. It also allows for incompatible substances to be separated until such times as they are released or, indeed, to keep substances completely separated, delivering said principles to distinct sites.

Moreover, it allows for the simplification of a treatment regime. The delivery devices 1; 11; 21 provide means for controlling complicated treatment regimes and removing some or all of the onus from

WO 02/07710

PCT/GB01/03247

- 22 -

the patient. In some therapies, cocktails of drugs are prescribed which have to be taken at set times, after meals for example, or in pre-determined patterns. Use of the inventive delivery devices 1; 11; 21 allows for drastic simplification of that procedure which may have profound effects in, for example, rural locations of developing countries where literacy rates may be low and clinicians are not on hand to supervise every aspect of a patient's treatment.

Moreover, in the treatment of animals such simplification of administration regimes is desired. For example, it may be difficult or arduous to repetitively administer medicaments to animals to treat a particular complaint. The inventive delivery devices 1; 11; 21 provide means to simplify that procedure, ensuring that the animal receives the desired dose of medicament whilst minimising the number of times a vet, for example, has to visit the animal and simplifying the treatment regime.

In, certain medical or other uses, time and one or more prevailing environmental conditions may affect the release rate. For example, the acidity of the stomach may partially control the release rate.

It is clear, therefore, that the inventive delivery devices 1; 11; 21 and associated methods provide means of delivering active principles and other components to a desired site by control of a few simple parameters. It should be understood that

WO 02/07710

PCT/GB01/03247

- 23 -

although the invention has been described with reference to the above examples, the ambit of the invention is to be determined by the appended claims.

5

It is to be appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment.

10 Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination.

WO 02/07710

PCT/GB01/03247

-24-

CLAIMS

1. An active principle delivery device comprising an inner capsule within an outer capsule, wherein:
5 the inner and outer capsules contain the same active principle;

 at least the outer capsule is a hard
10 capsule; and

 the active principle in at least one of the capsules comprises a fluid (as hereinbefore defined)
15
2. A delivery device according to claim 1, wherein at least a portion of the active principle is a fluid either at or immediately prior to its time of use or during its manufacture.
20
3. A delivery device according to claim 2, wherein the fluid is a liquid which comprises a solution and/or a suspension of the active principle.
- 25 4. A delivery device according to claim 3, wherein the liquid is thermosoftening.
5. A delivery device according to any of claims 1 to 4 wherein at least the outer capsule comprises
30 gelatin, plasticised gelatin, hydroxy propyl methyl cellulose (HPMC), starch or agar.
6. A delivery device according to any of claims 1 to 5, wherein at least one of the inner and outer
35 capsules is coated or uncoated in accordance with

WO 02/07710

PCT/GB01/03247

-25-

a desired release profile of active principle.

- 5 7. A delivery device according to any preceding
 claim, wherein the active principle comprises a
 fluid suspended solid.
- 10 8. A delivery device according to claim 7, wherein
 the fluid - suspended solid comprises a powder, a
 pellet, granules or any combination thereof.
- 15 9. A delivery device according to claim 7 or 8,
 wherein the fluid suspended solid is coated or
 uncoated in accordance with a desired release
 profile of active principle
- 20 10. A delivery device according to any preceding
 claim, wherein at least one of the inner and
 outer capsules contains the active principle in
 more than one phase.
- 25 11. A delivery device according to any preceding
 claim comprising more than one inner capsule
 within the outer hard capsule, the inner capsules
 being arranged in parallel and/or in series.
- 30 12. A delivery device according to any preceding
 claim which provides a pharmaceutical dosage form
 for the administration of the same active
 principle in single therapies.
- 35 13. A delivery device according to any preceding
 claim, wherein the active principle comprises a
 medicinal or nutritional product.
14. A delivery device according to any preceding

WO 02/07710

PCT/GB01/03247

-26-

claim further comprises an activator or co-reactant for the active principle.

- 5 15. A method of fabricating an active principle delivery device, comprising:

providing a first capsule and a second capsule of which at least the first capsule is a hard capsule;

10

placing the same active principle in each of the first and second capsules, with the active principle in at least one of the capsules comprising a fluid (as hereinbefore defined); and

15

placing the second, active principle - containing capsule within the first, active principle - containing, hard capsule.

20

16. A method according to claim 15, wherein at least a portion of the active principle is a fluid either at or immediately prior to its time of use or during its manufacture.

25

17. A method according to claim 15 or 16 wherein at least the first hard capsule comprises gelatin, plasticised gelatin, hydroxy propyl methyl cellulose (HPMC), starch or agar.

30

18. A method according to claim 15, 16 or 17, wherein at least one of the first and second capsules is coated or uncoated in accordance with a desired release profile of active principle.

WO 02/07710

PCT/GB01/03247

-27-

19. A method according to any of claims 15 to 18,
wherein the fluid is a liquid which comprises a
solution and/or a suspension of active principle.
- 5 20. A method according to claim 19, wherein the
liquid is thermosoftening.
- 10 21. A method according to any of claims 15 to 20,
wherein the active principle comprises a fluid -
suspended solid.
- 15 22. A method according to claim 21, wherein the fluid
- suspended solid comprises a powder, a pellet,
granules or any combination thereof.
- 20 23. A method according to claim 21 or 22 further
comprising formulating a desired release profile
of active principle and providing the suspended
solid in coated or uncoated form, such that the
release thereof accords with the desired release
profile.
- 25 24. A method according to claim 23, wherein the
desired release profile is determined by a
nominal or theoretical pharmaco-kinetic profile
of the active principle.
- 30 25. A method according to any of claims 15 to 24,
wherein at least one of the first and second
capsules contains the active principle in more
than one phase.
26. A method according to any of claims 15 to 25,

WO 02/07710

PCT/GB01/03247

-28-

wherein more than one second capsule is placed within the first, hard capsule, the second capsules being arranged in parallel and/or in series.

5

27. A method according to any of claims 15 to 26 further comprising providing a pharmaceutical dosage form for the administration of the same active principle in single therapies.

10

28. A method according to any of claims 15 to 27, wherein the active principle comprises a medicinal or nutritional product.

15

29. A method according to any of claims 15 to 28 further comprising providing an activator or co-reactant for the active principle within the delivery device.

20

30. A method of controlling the pharmaco-kinetic profile of an active principle comprising the steps of:

25

determining a first efficacious site for active principle release;

placing an active principle in a first hard capsule;

30

placing the same active principle in a second capsule within the active - principle - containing, , first hard capsule, with the active principle in at least one of the first and second capsules comprising a fluid (as hereinbefore defined)

35

WO 02/07710

PCT/GB01/03247

- 29 -

5 delivering the delivery device to the
 predetermined site; and

5

 controlling the release of the active
 principle at the site.

10 31. A method according to claim 30 further
 comprising:

 determining a second efficacious site for
 active principle release;

15

 delivering at least a portion of the
 delivery device to the second site
 subsequent to the delivery of said device to
 the first site; and

20

 controlling the release of active principle
 at the second site.

25 32. A method according to claim 30 or 31, wherein the
 active principle comprises a medicinal or
 nutritional product.

30 33. A method according to claim 30, 31 or 32, wherein
 said control of the release of the active
 principle is afforded by the dissolution
 characteristics of at least one of the first and
 second capsules.

WO 02/07710

PCT/GB01/03247

1/2

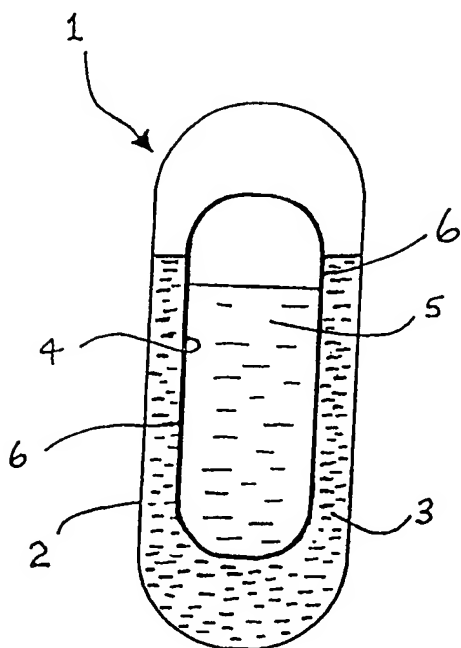


FIGURE 1

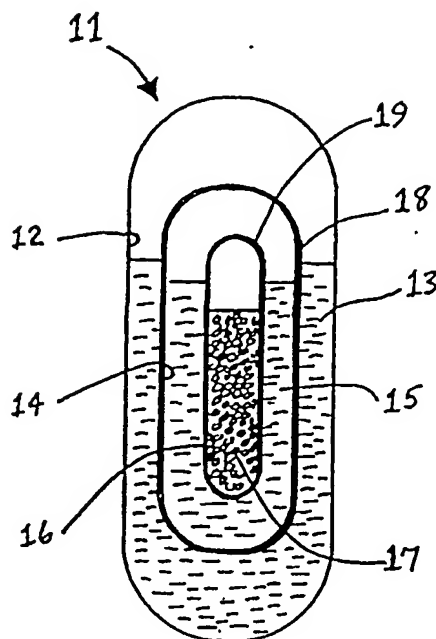


FIGURE 2

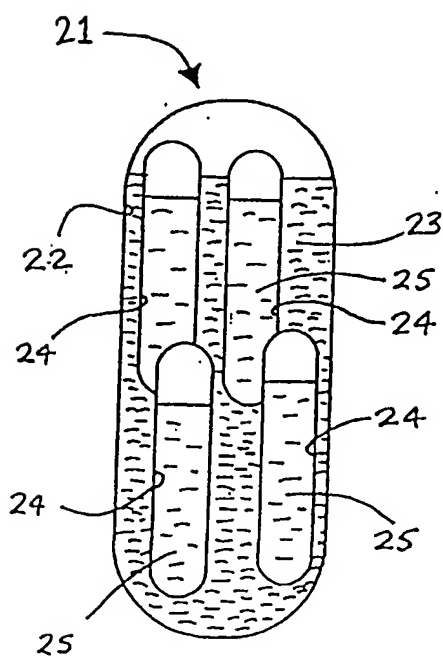


FIGURE 3

WO 02/07710

PCT/GB01/03247

2/2

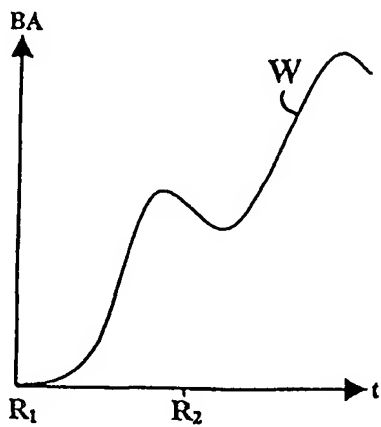


Figure 4A

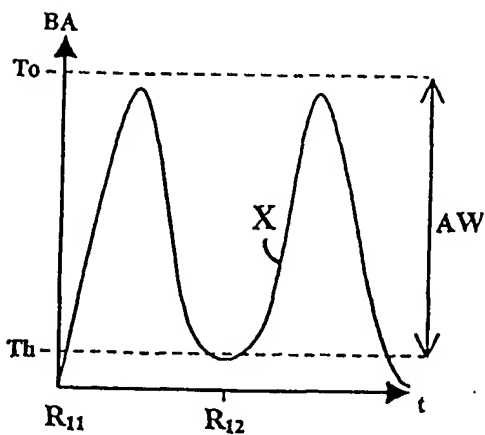


Figure 4B

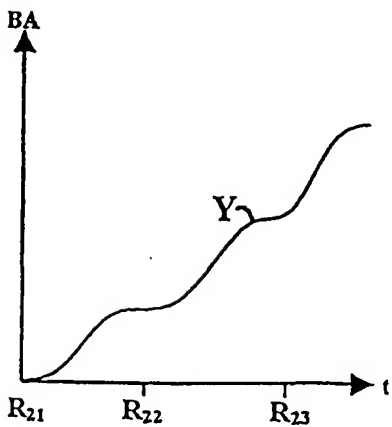


Figure 4C

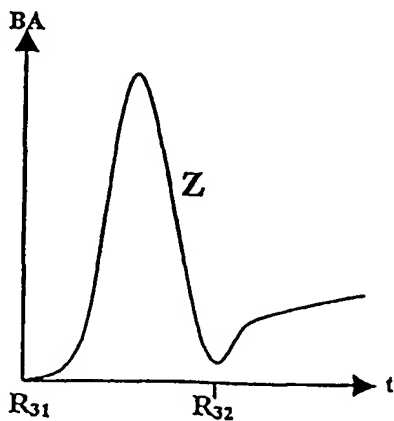


Figure 4D